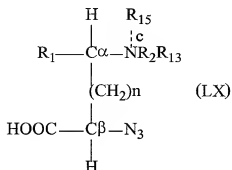


What is claimed is:

1. A non-natural amino acid compound having the formula LX:



wherein

n is an integer of from 1 to 4;

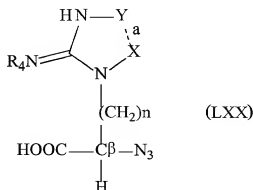
R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>13</sub>, and R<sub>15</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>α</sub> and C<sub>β</sub> are carbon atoms and the stereochemistry at C<sub>α</sub> and C<sub>β</sub> is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line c is present, then R<sub>15</sub> is present, and when dashed line c is not present, then R<sub>15</sub> is not present; wherein when dashed line c is present, the compound is a salt comprising a counterion.

2. The compound of claim 1, wherein the stereochemistry at C<sub>β</sub> is S.
3. The compound of claim 1, wherein R<sub>1</sub>, R<sub>2</sub>, and R<sub>13</sub> are, independently, hydrogen or methyl, and R<sub>15</sub> is methyl.
4. A non-natural amino acid compound of the formula LXX:



wherein

n is an integer of from 2 to 4;

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

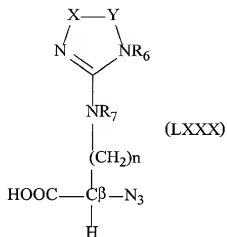
## ATTORNEY DOCKET NO. 19113.0083U4

R<sub>4</sub> is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>9</sub> is a carbon atom and the stereochemistry at C<sub>9</sub> is either R or S;

or the ester or salt thereof.

5. A non-natural amino acid compound of the formula LXXX:



wherein

n is an integer of from 2 to 4;

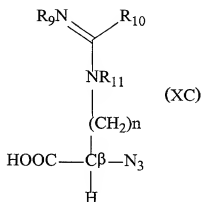
X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>6</sub> and R<sub>7</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;

or the ester or salt thereof.

6. A non-natural amino acid compound of the formula XC:



wherein

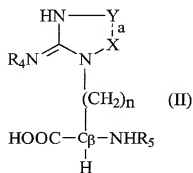
n is an integer of from 2 to 4;

$\text{R}_9$ ,  $\text{R}_{10}$ , and  $\text{R}_{11}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1$ - $\text{C}_5$ ; and

$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;  
or the ester or salt thereof.

7. A peptide comprising the non-natural amino acid of claim 1.

8. A peptide comprising the non-natural amino acid of claim 4.
9. A peptide comprising the non-natural amino acid of claim 5.
10. A peptide comprising the non-natural amino acid of claim 6.
11. A method for screening a peptide containing a non-natural amino acid compound for an activity, comprising the steps of:
  - a) measuring a known activity or pharmacological activity of a peptide having a known amino acid sequence comprising at least one natural amino acid; and
  - b) measuring the same activity or pharmacological activity of a peptide having the same amino acid as in step (a), with the exception that at least one natural amino acid is substituted with a non-natural amino acid having the formula II, LX, LXX, LXXX, and/or XC:



wherein

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n is an integer of from 2 to 4;

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>4</sub> and R<sub>5</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof, wherein

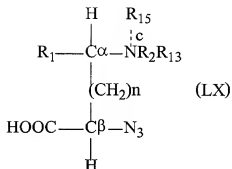
when n is 3, dashed line a is not present, R<sub>4</sub>, X and Y are all hydrogen, and R<sub>5</sub> is methyl, then C<sub>β</sub> is not S,

when n is 3, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are methyl, then the stereochemistry at C<sub>β</sub> is not R,

when dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then n is not 3,

when n is 4, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are the same lower branched or straight chain alkyl, then C<sub>β</sub> is not R, and

when n is 4, dashed line a is present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then the stereochemistry at C<sub>β</sub> is not R;



wherein

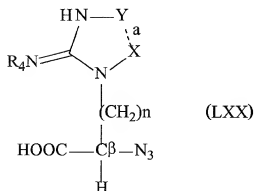
n is an integer of from 1 to 4;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>13</sub>, and R<sub>15</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>α</sub> and C<sub>β</sub> are carbon atoms and the stereochemistry at C<sub>α</sub> and C<sub>β</sub> is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line c is present, then R<sub>15</sub> is present, and when dashed line c is not present, then R<sub>15</sub> is not present; wherein when dashed line c is present, the compound is a salt comprising a counterion;



wherein

n is an integer of from 2 to 4;

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

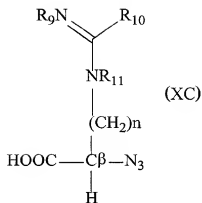
R<sub>4</sub> is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof;







wherein

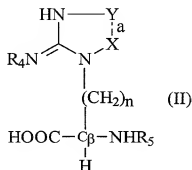
n is an integer of from 2 to 4;

R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>3</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S; or the ester or salt thereof.

12. The method of claim 11, wherein the compound is substituted for the comparable at least one natural amino acid of lysine and/or arginine.
13. The method of claim 11, wherein the pharmacological activity is half-life, solubility, or stability.
14. The method of claim 11, wherein the pharmacological activity is body barrier passage.

15. The method of claim 11, wherein the pharmacological activity is selectivity.
16. A method of treating or preventing in a subject a disease treated or prevented by the administration of a peptide containing a natural amino acid, comprising administering to the subject the known therapeutic peptide having, substituted for the natural amino acid, at least one non-natural amino acid having the formula II, LX, LXX, LXXX, and/or CX:



wherein

$n$  is an integer of from 2 to 4:

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is  $(CH_2)_z$ , wherein z is an integer of from 2 to 4;

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R<sub>4</sub> and R<sub>5</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof, wherein

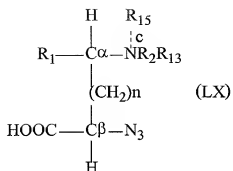
when n is 3, dashed line a is not present, R<sub>4</sub>, X and Y are all hydrogen, and R<sub>5</sub> is methyl, then C<sub>β</sub> is not S,

when n is 3, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are methyl, then the stereochemistry at C<sub>β</sub> is not R,

when dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then n is not 3,

when n is 4, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are the same lower branched or straight chain alkyl, then C<sub>β</sub> is not R, and

when n is 4, dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then the stereochemistry at C<sub>β</sub> is not R;



wherein

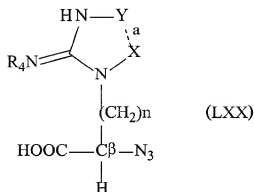
n is an integer of from 1 to 4;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>13</sub>, and R<sub>15</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>α</sub> and C<sub>β</sub> are carbon atoms and the stereochemistry at C<sub>α</sub> and C<sub>β</sub> is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line c is present, then R<sub>15</sub> is present, and when dashed line c is not present, then R<sub>15</sub> is not present; wherein when dashed line c is present, the compound is a salt comprising a counterion;



wherein

n is an integer of from 2 to 4;

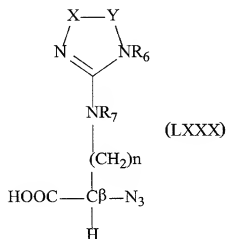
when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>4</sub> is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof;



wherein

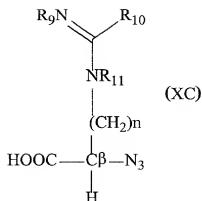
n is an integer of from 2 to 4;

X-Y is  $(CH_2)_z$ , wherein z is an integer of from 2 to 4;

$R_6$  and  $R_7$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ; and

$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;

or the ester or salt thereof; or



wherein

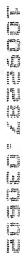
n is an integer of from 2 to 4;

R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S; or the ester or salt thereof.

17. The method of claim 16, wherein the natural amino acid is lysine and/or arginine.
18. A method of increasing the ability of a peptide to cross a body barrier of a subject, comprising substituting for at least one natural amino acid in the peptide at least one non-natural amino acid compound having the formula II, III, IV, LX, LXX, LXXX, and/or XC:



[illegible][illegible][illegible]

<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>14</b>	<b>15</b>	<b>16</b>	<b>17</b>	<b>18</b>	<b>19</b>	<b>20</b>	<b>21</b>	<b>22</b>	<b>23</b>	<b>24</b>	<b>25</b>	<b>26</b>	<b>27</b>	<b>28</b>	<b>29</b>	<b>30</b>	<b>31</b>	<b>32</b>	<b>33</b>	<b>34</b>	<b>35</b>	<b>36</b>	<b>37</b>	<b>38</b>	<b>39</b>	<b>40</b>	<b>41</b>	<b>42</b>	<b>43</b>	<b>44</b>	<b>45</b>	<b>46</b>	<b>47</b>	<b>48</b>	<b>49</b>	<b>50</b>	<b>51</b>	<b>52</b>	<b>53</b>	<b>54</b>	<b>55</b>	<b>56</b>	<b>57</b>	<b>58</b>	<b>59</b>	<b>60</b>	<b>61</b>	<b>62</b>	<b>63</b>	<b>64</b>	<b>65</b>	<b>66</b>	<b>67</b>	<b>68</b>	<b>69</b>	<b>70</b>	<b>71</b>	<b>72</b>	<b>73</b>	<b>74</b>	<b>75</b>	<b>76</b>	<b>77</b>	<b>78</b>	<b>79</b>	<b>80</b>	<b>81</b>	<b>82</b>	<b>83</b>	<b>84</b>	<b>85</b>	<b>86</b>	<b>87</b>	<b>88</b>	<b>89</b>	<b>90</b>	<b>91</b>	<b>92</b>	<b>93</b>	<b>94</b>	<b>95</b>	<b>96</b>	<b>97</b>	<b>98</b>	<b>99</b>	<b>100</b>
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[illegible][illegible][illegible]

**ATTORNEY DOCKET NO. 19113.0083U4**

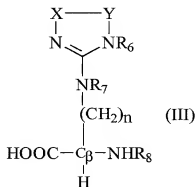
when n is 3, dashed line a is not present, R<sub>4</sub>, X and Y are all hydrogen, and R<sub>5</sub> is methyl, then C<sub>β</sub> is not S,

when n is 3, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are methyl, then the stereochemistry at C<sub>β</sub> is not R,

when dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then n is not 3,

when n is 4, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are the same lower branched or straight chain alkyl, then C<sub>β</sub> is not R, and

when n is 4, dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then the stereochemistry at C<sub>β</sub> is not R;



wherein

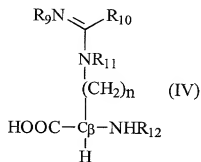
n is an integer of from 2 to 4;

X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

$R_6$ ,  $R_7$  and  $R_8$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1$ - $\text{C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof;



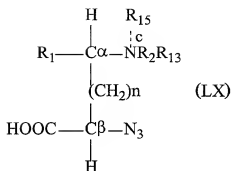
wherein

n is an integer of from 2 to 4;

$R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1$ - $\text{C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;  
or the ester or salt thereof;

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wherein

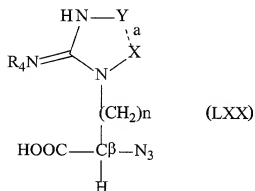
n is an integer of from 1 to 4;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>13</sub>, and R<sub>15</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>α</sub> and C<sub>β</sub> are carbon atoms and the stereochemistry at C<sub>α</sub> and C<sub>β</sub> is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line c is present, then R<sub>15</sub> is present, and when dashed line c is not present, then R<sub>15</sub> is not present; wherein when dashed line c is present, the compound is a salt comprising a counterion;



wherein

n is an integer of from 2 to 4;

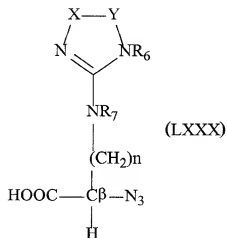
when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>4</sub> is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof;



wherein

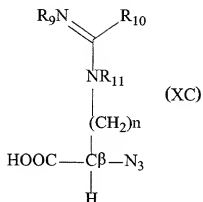
n is an integer of from 2 to 4;

X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

$\text{R}_6$  and  $\text{R}_7$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1$ - $\text{C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof; or



wherein

n is an integer of from 2 to 4;

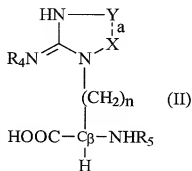
R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S; or the ester or salt thereof,

whereby the peptide having at least one non-natural amino acid is better able to cross the barrier than a peptide having no non-natural amino acid.

19. The method of claim 18, wherein the barrier comprises the blood brain barrier, a cell membrane, intestinal epithelium, skin, or blood-ocular.
20. The method of claim 18, wherein the barrier is the blood brain barrier.

21. The method of claim 18, wherein the natural amino acid comprises arginine and/or lysine.
22. The method of claim 18, wherein the compound comprises:
  - (a) a compound having the formula II, dashed line a is not present, n is 3, X, R<sub>4</sub>, and R<sub>5</sub> are hydrogen, Y is methyl, and the stereochemistry at C<sub>β</sub> is S;
  - (b) a compound having the formula II, dashed line a is not present, n is 3, X, R<sub>4</sub>, and R<sub>5</sub> are hydrogen, Y is ethyl, and the stereochemistry at C<sub>β</sub> is S;
  - (c) a compound having the formula II, dashed line a is present, n is 3, z is 2, R<sub>4</sub>, and R<sub>5</sub> are hydrogen, and the stereochemistry at C<sub>β</sub> is S; and
  - (d) a compound having the formula III, n is 3, X, R<sub>6</sub>, R<sub>7</sub>, and R<sub>8</sub> are hydrogen, and the stereochemistry at C<sub>β</sub> is S.
23. A method of increasing the selectivity of a peptide, comprising substituting for at least one natural amino acid at least one non-natural amino acid having the formula II, III, IV, LX, LXX, LXXX, and/or XC:





wherein

n is an integer of from 2 to 4;

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>4</sub> and R<sub>5</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof, wherein

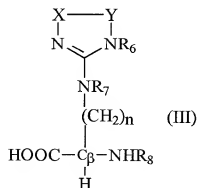
when n is 3, dashed line a is not present, R<sub>4</sub>, X and Y are all hydrogen, and R<sub>5</sub> is methyl, then C<sub>β</sub> is not S,

when n is 3, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are methyl, then the stereochemistry at C<sub>β</sub> is not R,

when dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then n is not 3,

when n is 4, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are the same lower branched or straight chain alkyl, then C<sub>β</sub> is not R, and

when n is 4, dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then the stereochemistry at C<sub>β</sub> is not R;



wherein

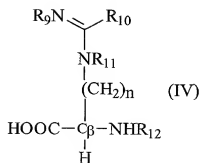
n is an integer of from 2 to 4;

X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof;

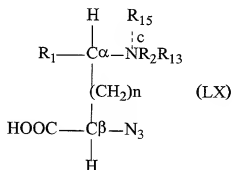


wherein

n is an integer of from 2 to 4;

R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S; or the ester or salt thereof;



wherein

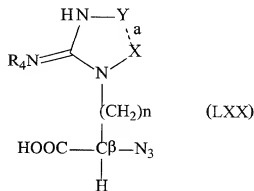
n is an integer of from 1 to 4;

$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{13}$ , and  $R_{15}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ; and

$C_\alpha$  and  $C_\beta$  are carbon atoms and the stereochemistry at  $C_\alpha$  and  $C_\beta$  is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line c is present, then  $R_{15}$  is present, and when dashed line c is not present, then  $R_{15}$  is not present; wherein when dashed line c is present, the compound is a salt comprising a counterion;



wherein

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n is an integer of from 2 to 4;

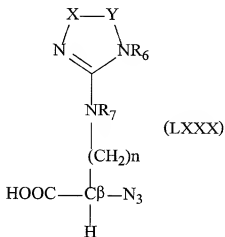
when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>4</sub> is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof;



wherein

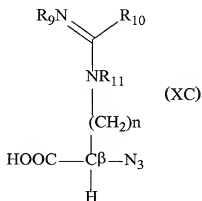
n is an integer of from 2 to 4;

X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

$\text{R}_6$  and  $\text{R}_7$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1\text{-C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof; or



wherein

n is an integer of from 2 to 4;

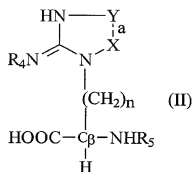
$\text{R}_9$ ,  $\text{R}_{10}$ , and  $\text{R}_{11}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1\text{-C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof,

whereby the peptide having at least one non-natural amino acid is more selective than the peptide having no non-natural amino acid.

24. The method of claim 23, wherein the natural amino acid comprises arginine and/or lysine.
25. A method of increasing the resistance of a peptide to digestion by a peptidase, comprising substituting for at least one natural amino acid in the peptide at least one non-natural amino acid having the formula II, III, IV, LX, LXX, LXXX, and/or XC:



wherein

n is an integer of from 2 to 4;

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

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when dashed line a is present, X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

R<sub>4</sub> and R<sub>5</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof, wherein

when n is 3, dashed line a is not present, R<sub>4</sub>, X and Y are all hydrogen, and R<sub>5</sub> is methyl, then C<sub>β</sub> is not S,

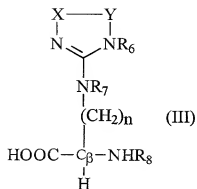
when n is 3, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are methyl, then the stereochemistry at C<sub>β</sub> is not R,

when dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then n is not 3,

when n is 4, dashed line a is not present, X and R<sub>5</sub> are hydrogen, and Y and R<sub>4</sub> are the same lower branched or straight chain alkyl, then C<sub>β</sub> is not R, and

when n is 4, dashed line a is not present, and R<sub>4</sub>, R<sub>5</sub>, X and Y are all hydrogen, then the stereochemistry at C<sub>β</sub> is not R;





wherein

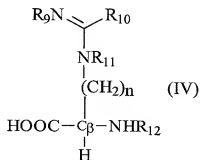
n is an integer of from 2 to 4;

X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

$\text{R}_6$ ,  $\text{R}_7$  and  $\text{R}_8$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1\text{-C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof;

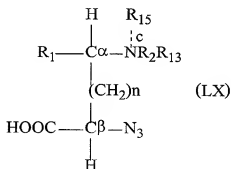


wherein

n is an integer of from 2 to 4;

R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S; or the ester or salt thereof;



wherein

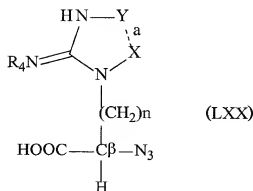
n is an integer of from 1 to 4;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>13</sub>, and R<sub>15</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>α</sub> and C<sub>β</sub> are carbon atoms and the stereochemistry at C<sub>α</sub> and C<sub>β</sub> is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line c is present, then  $R_{15}$  is present, and when dashed line c is not present, then  $R_{15}$  is not present; wherein when dashed line c is present, the compound is a salt comprising a counterion;



wherein

$n$  is an integer of from 2 to 4;

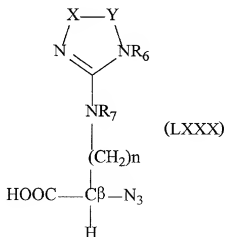
when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ;

when dashed line a is present, X-Y is  $(CH_2)_z$ , wherein  $z$  is an integer of from 2 to 4;

$R_4$  is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ; and

$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;

or the ester or salt thereof;



wherein

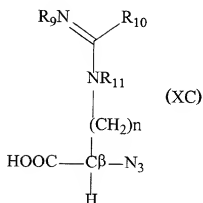
n is an integer of from 2 to 4;

X-Y is  $(CH_2)_z$ , wherein z is an integer of from 2 to 4;

$R_6$  and  $R_7$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ; and

$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;

or the ester or salt thereof; or



wherein

$n$  is an integer of from 2 to 4;

$\text{R}_9$ ,  $\text{R}_{10}$ , and  $\text{R}_{11}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1\text{-C}_5$ ; and

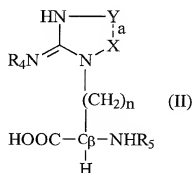
$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S; or the ester or salt thereof,

whereby the peptide having at least one non-natural amino acid is better able to resist digestion by a peptidase than a peptide having no non-natural amino acid.

26. The method of claim 25, wherein the natural amino acid comprises arginine and/or lysine.

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27. A method of treating or preventing in a subject a disease treated or prevented by the administration of a peptide that crosses a body barrier, comprising administering to the subject a peptide having, substituted for at least one natural amino acid at least one non-natural amino acid having the formula II, III, IV, LX, LXX, LXXX, and/or XC:



wherein

n is an integer of from 2 to 4;

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>4</sub> and R<sub>5</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof, wherein

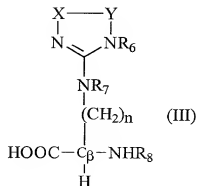
when n is 3, dashed line a is not present,  $R_4$ , X and Y are all hydrogen, and  $R_5$  is methyl, then  $C_\beta$  is not S,

when n is 3, dashed line a is not present, X and  $R_5$  are hydrogen, and Y and  $R_4$  are methyl, then the stereochemistry at  $C_\beta$  is not R,

when dashed line a is not present, and  $R_4$ ,  $R_5$ , X and Y are all hydrogen, then n is not 3,

when n is 4, dashed line a is not present, X and  $R_5$  are hydrogen, and Y and  $R_4$  are the same lower branched or straight chain alkyl, then  $C_\beta$  is not R, and

when n is 4, dashed line a is not present, and  $R_4$ ,  $R_5$ , X and Y are all hydrogen, then the stereochemistry at  $C_\beta$  is not R;



wherein

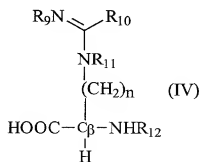
n is an integer of from 2 to 4;

X-Y is  $(CH_2)_z$ , wherein z is an integer of from 2 to 4;

$R_6$ ,  $R_7$  and  $R_8$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ; and

$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;

or the ester or salt thereof;



wherein

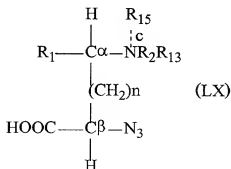
n is an integer of from 2 to 4;

$R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ; and



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$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;  
or the ester or salt thereof;



wherein

$n$  is an integer of from 1 to 4;

$\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_{13}$ , and  $\text{R}_{15}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1$ - $\text{C}_5$ ; and

$\text{C}_\alpha$  and  $\text{C}_\beta$  are carbon atoms and the stereochemistry at  $\text{C}_\alpha$  and  $\text{C}_\beta$  is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line  $c$  is present, then  $\text{R}_{15}$  is present, and when dashed line  $c$  is not present, then  $\text{R}_{15}$  is not present; wherein when dashed line  $c$  is present, the compound is a salt comprising a counterion;



wherein

$n$  is an integer of from 2 to 4;

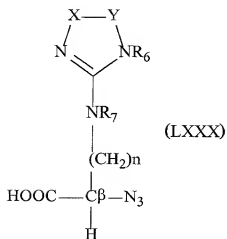
when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1-C_5$ ;

when dashed line a is present, X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

R<sub>4</sub> is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof;



wherein

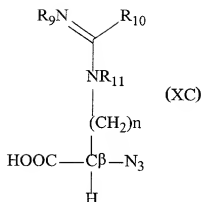
n is an integer of from 2 to 4;

X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

$\text{R}_6$  and  $\text{R}_7$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1\text{--C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof; or



wherein

n is an integer of from 2 to 4;

R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

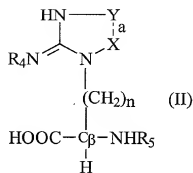
C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S; or the ester or salt thereof,

whereby the peptide having at least one non-natural amino acid crosses the body barrier in higher amounts than the peptide having no non-natural amino acid.

28. A method of treating or preventing in a subject a disease of the brain treated or prevented by the administration of a peptide containing a natural amino acid, comprising administering to the subject the known therapeutic peptide having, substituted for the natural amino acid, at least one non-

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natural amino acid having the formula II, III, IV, LX, LXX, LXXX, and/or XC:



wherein

n is an integer of from 2 to 4;

when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1\text{--C}_5$ ;

when dashed line a is present, X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

$\text{R}_4$  and  $\text{R}_5$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1\text{--C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof, wherein

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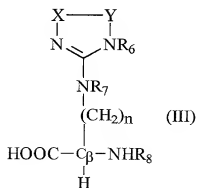
when n is 3, dashed line a is not present,  $R_4$ , X and Y are all hydrogen, and  $R_5$  is methyl, then  $C_\beta$  is not S,

when n is 3, dashed line a is not present, X and  $R_5$  are hydrogen, and Y and  $R_4$  are methyl, then the stereochemistry at  $C_\beta$  is not R,

when dashed line a is not present, and  $R_4$ ,  $R_5$ , X and Y are all hydrogen, then n is not 3,

when n is 4, dashed line a is not present, X and  $R_5$  are hydrogen, and Y and  $R_4$  are the same lower branched or straight chain alkyl, then  $C_\beta$  is not R, and

when n is 4, dashed line a is not present, and  $R_4$ ,  $R_5$ , X and Y are all hydrogen, then the stereochemistry at  $C_\beta$  is not R;



wherein

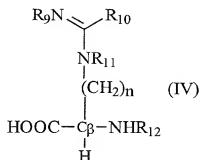
n is an integer of from 2 to 4;

X-Y is  $(\text{CH}_2)_z$ , wherein z is an integer of from 2 to 4;

$R_6$ ,  $R_7$  and  $R_8$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1$ - $\text{C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;

or the ester or salt thereof;

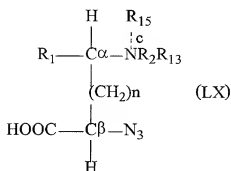


wherein

n is an integer of from 2 to 4;

$R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $\text{C}_1$ - $\text{C}_5$ ; and

$\text{C}_\beta$  is a carbon atom and the stereochemistry at  $\text{C}_\beta$  is either R or S;  
or the ester or salt thereof;



wherein

n is an integer of from 1 to 4;

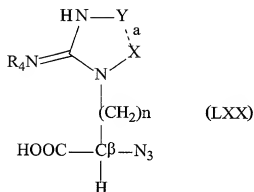
R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>13</sub>, and R<sub>15</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>α</sub> and C<sub>β</sub> are carbon atoms and the stereochemistry at C<sub>α</sub> and C<sub>β</sub> is, independently, either R or S;

or the ester or salt thereof,

wherein when dashed line c is present, then R<sub>15</sub> is present, and when dashed line c is not present, then R<sub>15</sub> is not present; wherein when dashed line c is present, the compound is a salt comprising a counterion;





wherein

n is an integer of from 2 to 4;

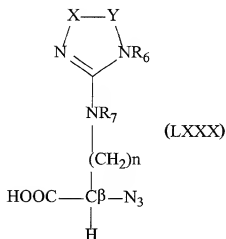
when dashed line a is not present, X and Y are independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>;

when dashed line a is present, X-Y is (CH<sub>2</sub>)<sub>z</sub>, wherein z is an integer of from 2 to 4;

R<sub>4</sub> is hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S;

or the ester or salt thereof;



wherein

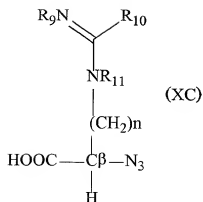
n is an integer of from 2 to 4;

X-Y is  $(CH_2)_z$ , wherein z is an integer of from 2 to 4;

$R_6$  and  $R_7$  are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of  $C_1$ - $C_5$ ; and

$C_\beta$  is a carbon atom and the stereochemistry at  $C_\beta$  is either R or S;

or the ester or salt thereof; or



wherein

n is an integer of from 2 to 4;

R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are, independently, hydrogen or lower branched or straight chain alkyl, alkenyl or alkynyl of C<sub>1</sub>-C<sub>5</sub>; and

C<sub>β</sub> is a carbon atom and the stereochemistry at C<sub>β</sub> is either R or S; or the ester or salt thereof.